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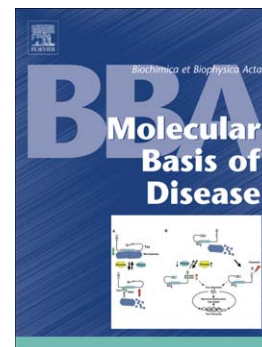
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**Dermatomyositis, polymyositis and immune-mediated necrotising myopathies**

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**Abstract**

Dermatomyositis, polymyositis and immune-mediated necrotising myopathy are major forms of idiopathic inflammatory myopathy. We review here recent developments in understanding of the pathology and pathogenesis of these diseases, and characterisation of autoantibody biomarkers. Dermatomyositis is traditionally considered to be due to a complement-mediated microangiopathy but the factors responsible for complement activation remain uncertain. Recent studies have emphasised the importance of the type I interferon pathway in the pathogenesis of the disease and have identified autoantibodies with specificities for different clinical subgroups of patients. Polymyositis is characterised by a cytotoxic T cell response targeting as yet unidentified muscle antigens presented by MHC Class I molecules, and can occur in isolation but is more often part of a multi-systemic overlap syndrome.

The immune-mediated necrotising myopathies are heterogeneous and are distinguished from polymyositis by the sparseness of inflammatory infiltrates and recognition of an association with specific autoantibodies such as anti-SRP and anti-HMGCR in many cases.

**Key words:** idiopathic inflammatory myopathy; polymyositis; dermatomyositis; immune-mediated necrotising myopathy; autoantibodies

**Highlights:**

- Complement-dependent microangiopathy and activation of the type I IFN pathway play major roles in DM
- CD8<sup>+</sup> T cell-mediated cytotoxicity is the cause of muscle injury in PM
- IMNM associated with anti-SRP antibody is complement-mediated
- IMNM associated with anti-HMGCR antibody can occur both in statin-treated and statin-naïve patients

**Abbreviations:** BAFF, B cell-activating factor; BLTK, B lymphoid tyrosine kinase; CCL21, chemokine (C-C motif) ligand 2; CK, creatine kinase; DC, dendritic cell; CTD, connective tissue disease; DFS70, dense fine speckled 70; DM, dermatomyositis; HIV, human immunodeficiency virus; HLA, human leukocyte antigen; HMGCR, 3-hydroxy-3-methyl-glutaryl-CoA reductase; HTLV-1, human T cell leukaemia virus; IBM, inclusion body myositis; IFIH1, interferon induced with helicase C domain protein 1; IL, interleukin; IMNM, immune-mediated necrotising myopathies; INF, interferon; IP-10, INF $\gamma$ -inducible 10-kd protein; ISG15, IFN-stimulated gene 15; I-TAC, IFN-inducible T cell  $\alpha$  chemoattractant; LEDGF, lens epithelium-derived growth factor; MAC, membrane attack complex; MCP-1, monocyte chemoattractant protein-1; MCTD, mixed connective tissue disease; MDA5, melanoma differentiation-associated gene 5; MHC, major histocompatibility complex; MIF, macrophage inhibition factor; MIP-1 $\alpha$ , macrophage inflammatory protein 1 $\alpha$ ;

miRNA, microRNA; MxA, myxovirus resistance 1 protein; NuRD, nucleosome remodelling deacetylase complex; NXP-2, nuclear matrix protein 2; pDC, plasmacytoid dendritic cell; PKC $\epsilon$ , protein kinase C  $\epsilon$  type; PLCL1, phospholipase C like-1; PM, polymyositis; PTPN, protein tyrosine phosphatase N22 gene; SRP, signal recognition particle; RNP, ribonuclear protein complex; TIF, transcription intermediary factor; TLR, Toll like receptor; TNF, tumour necrosis factor; VCAM1, vascular cell adhesion molecule 1; VEGF, vascular endothelial growth factor

## 1. Introduction

The idiopathic inflammatory myopathies (IIM) are currently classified into four major categories: dermatomyositis (DM), polymyositis (PM), inclusion body myositis (IBM) and the immune-mediated necrotising myopathies (IMNM). Although the clinical presentations of DM and PM are similar, manifesting usually as subacute painless proximal limb weakness, plus the distinctive skin manifestations of DM, immunopathologic observations and more recent gene expression and proteomic analyses have provided convincing evidence that the underlying pathogenetic mechanisms in these disorders are fundamentally different. An alternative method of classification based upon the major histopathological features in each condition has recently been proposed [1].

Polymyositis is generally regarded as a prototypic T cell mediated autoimmune myopathy, whereas DM has traditionally been attributed to a humoral-driven microangiopathy, although the putative autoantibodies and their targets have yet to be identified, and there is increasing evidence implicating the type I interferon pathway in the pathogenesis of the disease. In contrast, IBM is characterised clinically by a more selective pattern of muscle weakness, protracted clinical course and poor response to treatment, and pathologically by a combination of a T cell dominant inflammatory response and myofibre degeneration. The IMNMs are a heterogeneous group of necrotising myopathies, which in some cases are associated with specific autoantibodies such as anti-HMGCR and anti-SRP, but whose pathogenesis is still incompletely understood. The major clinical and pathological features of DM, PM and IMNM are summarised in Table 1.

This review provides an update on recent advances in our understanding of the cellular and molecular pathogenesis of DM, PM and IMNM, and progress in the characterisation of autoantibody biomarkers for the different subgroups of immune-mediated inflammatory myopathies. The pathogenesis of IBM, which is a distinctive disease given its additional myodegenerative features, has been reviewed elsewhere [2-4], and is dealt with in a separate review by Askanas and Engel in this issue.

Table 1: Clinical, serological and pathological features of immune-mediated inflammatory myopathies

	Dermatomyositis	Polymyositis	IMNM
Muscle weakness	Proximal predominant (UL>LL)	Proximal predominant	Proximal + distal
Skin involvement	+	-	-
Association with CTD	+	++	+
Association with malignancy	+	+	-
Association with viral infections (HIV, HTLV-1, hepatitis C)	+	+	+
Autoantibodies (target antigens)	Mi-2, MDA5, TIF-1, NXP-2	U1-snRNP, PM-Scl, Antisynthetase	SRP, HMGR
Histopathology			
Myofibre necrosis	Fibre groups, perifascicular, microinfarcts	Single fibres	Single fibres
Perifascicular atrophy	+	-	-
Inflammatory infiltrates	CD4+ T cells, B cells, pDCs (BDCA2+)	CD8+ T cells, plasma cells (CD138+), mDCs (BDCA1+)	Macrophages (CD68+/CD163+)
MAC (C5b-9)	++	-	+/-
MHC-I/II	++	++	+/-
Capillary depletion	++	+/-	-

## 2. Dermatomyositis

### 2.1 Clinical aspects

As shown in Table 2, DM can be classified into childhood and adult forms, and subgroups in which the cutaneous manifestations predominate and muscle weakness is minimal or absent (amyopathic DM), or there are systemic features, or the condition is associated with an underlying malignancy, or is part of an overlap syndrome. Although individual cases of DM can be classified into a particular category based on the presence and severity of skin and muscle involvement, it is likely that they are all part of a disease spectrum in which the skin and muscles are affected to a variable degree. When the typical DM rash is present on the face (heliotrope rash), hands and elbows (Gottron's papules), and trunk (shawl and V signs) it is diagnostic of the condition. There is usually a predominantly proximal pattern of muscle weakness, which may be more severe in the upper limbs, and in some cases is associated with myalgia and edema of the overlying skin. Subcutaneous calcinosis commonly occurs, particularly in childhood cases, but also in some adult cases [5, 6]. In some cases the skin changes may be transient or are relatively inconspicuous when the patient is first seen, and may only become obvious at a later stage. In such cases a mistaken diagnosis of PM or of a non-inflammatory myopathy may be made prior to muscle biopsy.

Table 2 Classification of dermatomyositis (DM) and associated autoantibodies

	Autoantibodies
Juvenile DM	Anti-NXP-2
Adult DM	Anti-Mi-2
DM with systemic manifestations	Anti-MDA5
DM with systemic manifestations	Anti-SAE
Cancer-associated DM	Anti-TIF-1 $\gamma$ , TIF-1 $\alpha$
Amyopathic DM	Anti-MDA5

### 2.2 Immunopathology



DM is traditionally considered to be an ischemic myopathy resulting from a complement (C5b-9) mediated injury to endothelial cells leading to depletion of the muscle capillary bed and to muscle fibre necrosis and the characteristic perifascicular pattern of muscle fibre atrophy [7]. However, it remains unclear how the complement pathway is activated in DM and autoantibodies targeting endothelial cell antigens have never been identified. The inflammatory cells in the perimysial and perivascular infiltrates comprise mainly B cells and CD4+ T helper cells [8] including interferon- $\alpha$  (IFN $\alpha$ ) producing plasmacytoid dendritic cells, IFN $\gamma$  producing Th1 cells and interleukin 17 (IL-17) producing Th17 cells (Fig 1) [9, 10]. The activation of CD4+ T cells may involve the expression of Toll like receptors (TLR) 4 and 9 [11]. IL-17 is thought to facilitate the migration of mononuclear cells to muscle as well as inducing up-regulation of muscle membrane MHC-I molecules [12]. B cell-activating factor (BAFF), which is involved in the maintenance of mature B cells and plasma cells, is also up-regulated [13]. It is postulated that deposition of immunoglobulins on intramuscular capillaries activates the complement cascade, triggering the production of pro-inflammatory cytokines and chemokines, which in turn up-regulate the expression of adhesion molecules on endothelial cells leading to further recruitment of B cells, T cells and macrophages and stimulation of plasmacytoid dendritic cells [5, 14].

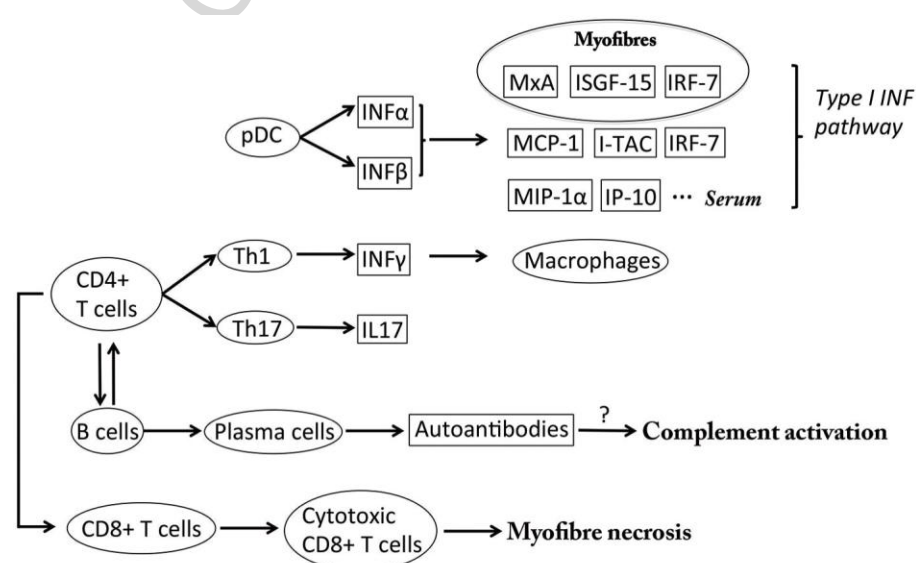


Figure 1 Schematic representation of the involvement of CD4<sup>+</sup> and CD8<sup>+</sup> T cells, B cells and the Th1, Th17 and type I interferon pathways in inflammatory myopathies. Plasmacytoid dendritic cells (pDCs) produce type I interferons (INF $\alpha/\beta$ ), which results in up-regulated expression of INF-stimulated genes in muscle (MxA, ISGF-15, IRF-7...) and blood (I-TAC, IRF-7, IP-10, MCP-1...) in DM. The differentiation of CD4<sup>+</sup> T cells is polarized to Th1 and Th17 responses, the former activating macrophages and the latter producing the pleiotropic cytokine IL17. CD4<sup>+</sup> T cells are also necessary for the differentiation of B cells and antibody production. A Th1 response is thought to be primarily involved in IMNM [15], while in PM and IBM CD8<sup>+</sup> T cells are the primary effector cells.

### *2.1 Type I interferon pathway*

Since the finding that interferon inducible genes are highly up-regulated in DM tissues [16], the importance of the type I IFN pathway has been under the spotlight. Subsequent studies demonstrated strong expression of the type I IFN inducible proteins ‘human myxovirus resistance 1 protein’ (MxA) and ‘IFN-stimulated gene 15’ (ISG15) in DM muscle, particularly in capillaries and perifascicular muscle fibres [17]. It has also been shown that blood, muscle and skin all share the same ‘type I IFN signature’ of gene expression in DM [18]. Moreover, serum levels of IFN $\alpha$ , IFN $\beta$  and several type I IFN-regulated proteins (IFN-inducible  $\alpha$  T cell chemoattractant, IFN- $\gamma$ -inducible 10-kD protein, monocyte chemotactic protein 1 and 2), as well as the pro-inflammatory cytokine IL-6, are increased in DM and are potential biomarkers of disease activity [19-21]. Interestingly, IFN $\beta$ , but not IFN $\alpha$ , was found to be associated with up-regulation of IFN-related genes in serum [22] and in muscle tissue, more so in juvenile than adult DM [23]. Moreover, DM sera with nucleic acid-associated antibodies were found to activate the IFN $\alpha$  expression, suggesting that up-regulation of type I IFN may be secondary to the production of autoantibodies [24].

While the up-regulation of type I IFN in DM is undisputable, its significance and specificity in the pathogenesis of the disease remains to be decided. For example, in a study comparing type I IFN and other cytokine signatures (e.g. granulocyte-monocyte colony-stimulating factor, IL-10, IL-13, IL-1 $\beta$  and TNF $\alpha$ ), although the type I IFN

signature in blood was the most markedly up-regulated in inflammatory myopathies, type I IFN expression levels were comparable in DM and PM [25]. Similarly, the pattern of type I IFN signature in the skin in DM was similar to that seen in systemic lupus erythematosus and herpes simplex virus-2 virus infection [26]. Moreover, whether and how the accumulation of IFN-inducible proteins contributes to the perifascicular atrophy and muscle fibre injury remains to be determined. Type I IFNs may lead to over-expression of MHC-I molecules (Fig 2) which may have pathogenic effects in their own right through induction of endoplasmic reticulum stress and the unfolded protein response in muscle fibres [27, 28].

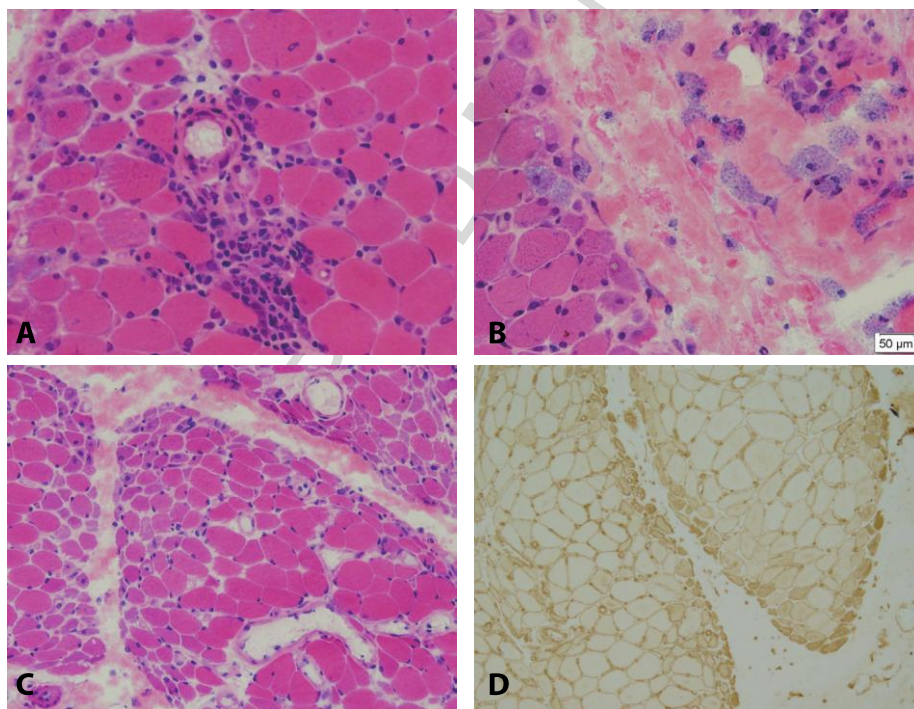


Figure 2 Dermatomyositis: A. Endomysial and perivascular mononuclear inflammatory infiltrate; B. Fragmentation of perimysial connective tissue and infiltration with granular mononuclear cells and macrophages; C & D perifascicular fibre regeneration and atrophy. A-C: haematoxylin and eosin stain; D: MHC-I immunohistochemistry.

## 2.2 Microvascular pathology

The early studies of De Visser et al (1989) and Emslie-Smith and Engel (1990) showed that membrane attack complex (MAC) deposition and degenerative changes in intramuscular capillaries, and depletion of capillary numbers, occur even before other structural changes in the muscle [29, 30]. Subsequent studies have confirmed the capillary depletion which is associated with increased activation of endothelial cells and increased expression of vascular endothelial growth factor (VEGF) in muscle fibres [31, 32]. It has been shown that perimysial intermediate-sized vessels are also affected and are closely associated with regions of perifascicular fibre atrophy [33]. A recent study using 3D-reconstruction of microvessels in serial sections of DM muscles, including amyopathic cases, has demonstrated that rather than random loss of capillaries, it is the whole microvascular unit, that includes 6-8 endomysial capillaries branching from a terminal arteriole, that is lost [34]. On the basis of these findings the authors concluded that muscle ischaemia probably results from inflammatory narrowing of perimysial arcade arteries and that activation of the complement cascade in endomysial capillaries may be secondary to ischaemic-reperfusion injury.

The 250Å tubuloreticular inclusions in vascular endothelial cells, first described by Banker [35], are found both in juvenile and adult DM, and are generally regarded as a reliable marker for distinguishing DM from other inflammatory myopathies [36], although they have also been reported in myositis with overlap syndrome [37]. The origin of these structures is uncertain, but may be related to the effects of IFN $\alpha$  which is expressed in capillaries in DM and PM [9, 38] and has been shown to induce the formation of tubuloreticular inclusions in lymphocytes *in vitro* [39].

### 2.3 Autoantibodies

A number of autoantibodies have a high specificity for DM, but their role in the pathogenesis of the muscle damage remains unclear. One of the best and earliest recognised is anti-Mi-2 which is directed against a component of the nucleosome remodelling deacetylase complex (NuRD) [40, 41]. Anti-Mi-2 occurs mainly in adult cases, and is rare in juvenile DM [42]. Patients with anti-Mi-2 tend to have typical DM skin changes, higher serum CK levels and a good response to treatment, and are less likely to develop interstitial lung disease or cancer [43]. The reported frequency

of anti-Mi-2 antibodies varied greatly (3-60%) in DM cohorts from different geographic regions [43, 44] and was found to correlate with the level of ultraviolet light exposure in a large multicentre international study and in a study from the United States [44-46]. However, this was not confirmed in a more recent study from Central America [43]. A link with ultraviolet light exposure was supported by the finding of elevated levels of Mi-2 in cultured keratinocytes after exposure to ultraviolet B light [46]. Increased expression of Mi-2 was demonstrated in regenerating muscle fibres in DM biopsies, and it has been proposed that high levels of expression of the antigen in regenerating cells in muscle and epidermis may play a part in sustaining the autoimmune process [41]. Other myositis specific antibodies are rare in DM, with the exception of anti-Jo-1 which was present in up to 16% of adult cases in a large multicentre European study [47].

A number of newer autoantibodies which appear to be associated with particular subgroups of DM cases have been characterised in recent years (Table 2). Antibodies to the 155/140kDa nuclear proteins were first shown to be associated with DM and a higher risk for cancer [48], and this has been confirmed in a recent review and meta-analysis of published series [49]. The two proteins have been identified as transcription intermediary factor 1 $\gamma$  and 1 $\alpha$  respectively (TIF-1 $\gamma$ , TIF-1 $\alpha$ ), with an additional less frequent antigen TIF-1 $\beta$  from the same family [50]. Anti-TIF-1 antibodies occur in both juvenile and adult DM patients, with a positivity rate of 16-23% [43, 50, 51] and adult patients have a higher incidence of malignancy, whereas juvenile and young adult patients do not [43, 50]. It has been proposed that the TIF proteins are implicated in carcinogenesis and that anti-TIF-1 antibodies generated as part of an anti-tumour response may cross-react with other tissues such as muscle and skin expressing high levels of the antigens, and thereby propagate the autoimmune process [41].

An association with antibodies to CADM-140 (now termed MDA5) was first described in Japanese patient cohorts with clinically amyopathic DM and interstitial lung disease [52], and subsequently also in other racial groups [53-55]. The antibody recognises 'interferon induced with helicase C domain protein 1' (IFIH1), now known as 'melanoma differentiation-associated gene 5' (MDA5) [56, 57], which is a

cytoplasmic RNA-specific helicase belonging to the RIG-I-like receptor family. MDA5 participates in the innate immune response to viruses and is also a potential activator of type I IFN transcription. Subsequent studies of patients with anti-MDA5 antibodies have shown that they have more severe skin manifestations, a higher incidence of rapidly progressive interstitial lung disease, less muscle involvement and lower serum creatine kinase (CK) levels [54, 58]. However, there appears to be considerable racial and ethnic variation in the frequency of anti-MDA5 and in the associated clinical phenotype. In a recent report from the USA, only 6.9% of DM patients had anti-MDA5 antibodies, and most of these had overt myopathy with interstitial lung disease and a clinical phenotype resembling the antisynthetase syndrome [59].

Antibodies to the nuclear matrix protein 2 (NXP-2) (originally termed anti-MJ) are present in up to 25% of cases of juvenile DM and are associated with more severe muscle weakness, calcinosis, joint contractures and intestinal vasculitis [60-63]. Anti-NXP-2 antibodies were also found in 30% of adult DM cases in an Italian cohort [64], being more common in patients of younger age, but were present in only 1.6% of cases in a large Japanese series [65]. These findings again highlight the considerable racial and geographic differences in the frequencies of DM associated antibodies which are also known to be influenced by genetic factors, particularly the HLA genotype [66, 67].

Anti-small-ubiquitin-like-modifier-activating-enzyme (anti-SAE) antibodies are reported to have a prevalence of 8% in Caucasian and 1.8% in Asian DM patients [68, 69]. The clinical spectrum of patients with anti-SAE antibodies does not seem to be different from those without anti-SAE antibodies. However, the former have a higher representation of *HLA-DRB1\*04-DQA1\*03-DQB1\*03* genotype [69].

In contrast to the aforementioned autoantibodies, the prevalence of anti-dense fine speckled 70 antibodies (anti-DFS70) has been reported to be lower in DM than in normal individuals [70]. It is of interest that in this Japanese cohort, of the four patients with both anti-MDA5 and anti-DFS70 antibodies, three patients showed decreased anti-MDA5 and increased anti-DFS70 antibody levels during remission, while in the fourth patient who died anti-MDA titres were unchanged and anti-DFS70

antibody levels were essentially negative. It is tempting to speculate that anti-DFS70 antibodies, which target the lens epithelium-derived growth factor (LEDGF), may be protective against the development of DM [6].

#### 2.4 Genetic susceptibility

Similar to IBM, DM also shows a predisposition for specific human leukocyte antigen (*HLA*) genotypes, but to different alleles. *HLA-DQA1\*0501* is associated with increased susceptibility to juvenile DM [42]. The *tumour necrosis factor alpha* (*TNF $\alpha$* ) gene lies between the *HLA-B* and *HLA-DR3* loci. An A/G polymorphism in the promoter region of *TNF $\alpha$*  that leads to augmented *TNF $\alpha$*  production is highly represented in both juvenile and adult DM [44, 71]. A pilot study on 33 DM patients identified several single nucleotide polymorphisms in *IL-10* in association with DM [72]. A recent large genome-wide association study has confirmed the strong association with the *major histocompatibility complex* (*MHC*) region in both juvenile and adult cases of DM, and also demonstrated an association with polymorphisms in three other non-*MHC* genes previously associated with other autoimmune diseases, *phospholipase C like-1* (*PLCL1*), *B lymphoid tyrosine kinase* (*BLTK*), and *chemokine (C-C motif) ligand 21* (*CCL21*) [46]. Taken together, the majority of genes linked to an increased susceptibility for DM are involved in the inflammatory process, illustrating the pivotal role of inflammation in DM aetiology. Additionally, a polymorphism in the *protein tyrosine phosphatase N22 gene* (*PTPN*) is associated with juvenile DM but not adult DM [73].

A recent genome-wide DNA methylation profiling study of juvenile DM muscle biopsies has provided novel epigenetic data demonstrating altered methylation in a number of genes encoding transcription factors and cell cycle regulators [74]. These findings indicate the capacity for self-renewal in damaged muscles in juvenile DM, and that certain critical genes are epigenetically altered as a result of the disease process. Another study on IBM and PM presented evidence for increased cell cycle entry in these two diseases, possibly leading to activated cell apoptosis [75]. Whether DM has a similar profile of dysregulated cell cycle regulatory proteins awaits clarification.

### 2.5 Maternal microchimerism in childhood DM

It has been suggested that the presence of maternally derived cells in the circulation may contribute to the pathogenesis of multisystem autoimmune disease and may be comparable to the graft-vs-host disease which occurs after bone marrow transplantation in *HLA*-incompatible donors. In a cohort of 72 cases of juvenile DM maternal chimeric cells were identified in 83% of children with juvenile DM compared with 23% of unaffected siblings and 17% of healthy controls, and was associated with carriage by the mother of the *HLA-DQA1\*0501* allele which is a significant risk factor for juvenile DM [76]. In another study, evidence of maternal microchimerism was found in skin and muscle samples from 10/10 cases of juvenile DM compared with 2/10 cases of other muscle disorders [77]. These findings suggest that maternal chimerism may be involved in the pathogenesis of juvenile DM and warrants further investigation.

### 2.6 MicroRNAs

MicroRNAs (miRNAs) are a group of small noncoding RNAs that silence gene expression by base pairing with the 3' untranslated region of genes. Altered expression of miRNA has been found in DM, with miR-146b and miR-155 being the most up-regulated and miR-1, miR-133, miR-206, miR-11040 and miR-30a-3p down-regulated [78, 79]. However, the disturbance of miRNA expression is not unique to DM, as the majority of miRNAs with changed expression in DM also show similar trends in PM, IBM and muscular dystrophies. It is found that increased pro-inflammatory cytokines reduce the expression of miR-1, miR-133 and miR-206 that are involved in myoblast differentiation and muscle regeneration as well as CD4<sup>+</sup> helper T cell maturation, providing a novel link between inflammation and muscle damage via miRNA-mediated post-transcriptional regulation of gene expression [79, 80]. miR-126 inhibits the translation of vascular cell adhesion molecule 1 (VCAM1) and is repressed in serum and muscle of juvenile DM patients with a disease duration of under 2 months, suggesting the involvement of miR-126 in the recruitment of lymphocytes in the early stage of DM [81]. The level of miR-223, which inhibits the expression of protein kinase C  $\epsilon$  type (PKC $\epsilon$ ) that regulates multiple cellular processes, is reduced in skin tissues from DM patients, potentially leading to cell



proliferation in Gottron's papules [82]. miR-7 is also reduced in the serum and skin but its significance in the pathogenesis of DM requires further investigation [83].

### **3. Polymyositis**

#### *3.1 Clinical considerations*

The existence of PM as an isolated entity has been through vigorous debate, especially since the separation of IBM from PM [84-88]. The controversy relates to whether PM can occur as a primary muscle-specific disease or merely as part of a more widespread connective tissue disease or autoimmune disorder, considering their frequent coexistence. Although isolated PM is probably not as rare as has been suggested [88], several studies have found that it is the least common form when compared with DM and IBM [89-91] except in Japan where PM outnumbers the other varieties of IIM [91, 92].

PM typically manifests as a painless proximal myopathy with subacute onset and is usually responsive to corticosteroids and immune suppression. It occurs mainly in adults, but can occasionally present in childhood, although much more rarely than juvenile DM [93]. In addition to this classic phenotype there have also been reports of a distal variant which presents with weakness mainly in the upper limbs and a good response to treatment [94]. Other restricted variants include cases with dropped head or camptocormia due to involvement of the paraspinal muscles [95-98].

#### *3.2 Immunopathology*

Since the discovery of CD8<sup>+</sup> T cell predominant lymphocytes invading non-necrotic fibres in PM and IBM [99], the interaction of antigen-presenting MHC-I molecules (Fig 3) and effector CD8<sup>+</sup> T cell, and the subsequently activated cytotoxicity in terms of the release of perforin, has been considered the core pathogenic event in PM (Fig 1) [100]. CD8<sup>+</sup> T cells, but not CD4<sup>+</sup> T cells, clonally propagate in response to auto-antigens processed in muscle fibres and presented by surface MHC-I molecules [101-103]. It is worth mentioning that although the restricted clonal expansion indicates a limited number of antigens, the usage of adopted

complementarity-determining region seems to be different in different patients, raising doubt as to whether there is a common self-antigen in PM.

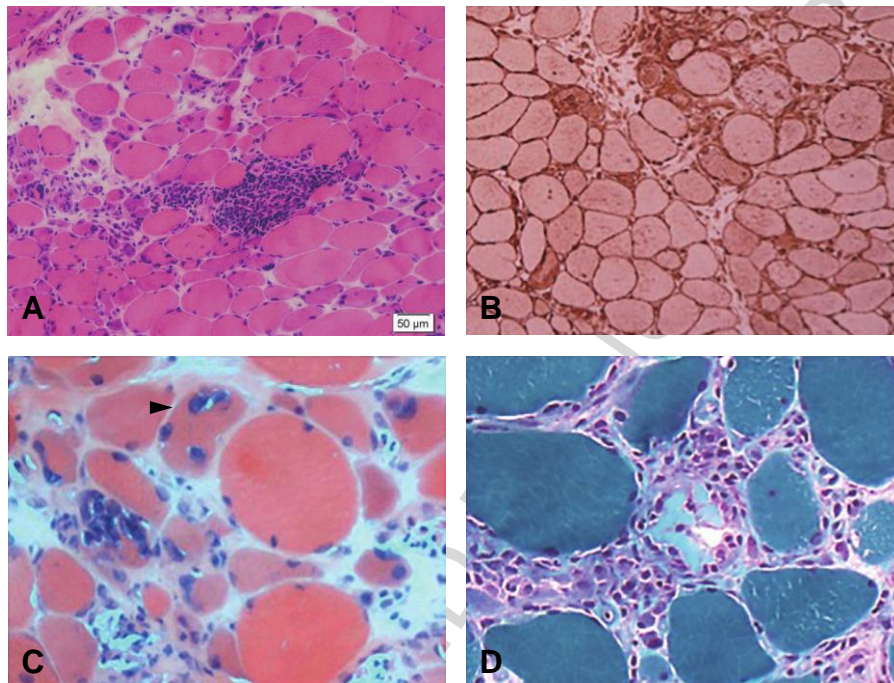


Figure 3 Polymyositis: endomysial mononuclear inflammatory infiltrate (A-D); myofibre invasion by mononuclear cells (C, arrowhead); myofibre necrosis (C, D); and diffuse MHC-I antigen expression (B). A & C: haematoxylin and eosin; B: MHC-I immunohistochemistry; D: Modified Gomori trichrome.

The interaction of Fas on muscle fibres and Fas ligand on invading CD4<sup>+</sup> T cells leads to cell apoptosis while expression of Bcl-2 is protective [104, 105]. The invading mononuclear cells have also been shown to include antigen-presenting BDCA-1<sup>+</sup> myeloid dendritic cells as well as antibody-secreting CD138<sup>+</sup> plasma cells [106, 107]. Another study identified that fascin-positive mature dendritic cells greatly predominate over langerin-positive immature dendritic cells in PM as well as DM, suggesting that the maturation of dendritic cells may take place outside the muscle rather than locally [108].

Although in both PM and IBM the infiltrating T cells are thought to proliferate and differentiate locally in muscle [109], findings in a myositis mouse model have shown

that CD8<sup>+</sup> T cells also proliferate in local draining lymph nodes [110]. The autoinvasive T cells and macrophages express monocyte chemoattractant protein-1 (MCP-1), which facilitates the recruitment of monocytes [111]. De Paepe showed the presence of pro-inflammatory chemokines as well as heat shock proteins and inducible nitric oxide synthase in proximity to the invaded muscle fibres, suggesting their involvement in the cytotoxicity of T cells [112]. The lysosomal cysteine protease cathepsin B, which is involved in antigen presentation by MHC-II [113], is also up-regulated in PM [114]. The pro-inflammatory cytokine, macrophage inhibition factor (MIF) is up-regulated and detected in necrotic and invaded non-necrotic PM muscle fibres, suggesting its participation in recruitment of macrophages as the initial step of muscle regeneration [115].

### *3.3 Fibroblasts*

In both PM and IBM, CD90<sup>+</sup> CD34<sup>+</sup> fibroblasts have also been shown to invade non-necrotic muscle fibres [116]. However, in PM the basement membrane is disrupted and the fibroblasts are in direct contact with the plasma membrane, whereas in IBM they are ensheathed by the basement membrane. The pathological impact of these invading fibroblasts in PM may be pro-inflammatory and they may contribute to the breakdown of the sarcolemma.

### *3.4 Microvascular changes*

It is of interest that muscle capillary numbers have been found to be reduced in the early stages of PM as well as DM, and VEGF, which promotes angiogenesis, is up-regulated [32]. The significance of these findings is unclear but they suggest that hypoxia may also play a part in the pathophysiology of PM.

### *3.5 Autoantibodies and overlap syndromes*

As shown in Table 1, PM can be associated with a number of different autoantibodies and other autoimmune disorders, and is then classified as belonging to one of the 'overlap syndromes'. The best characterised of these are: mixed connective tissue disease (MCTD), scleroderma-myositis overlap syndrome, and the antisynthetase syndrome, although as has been pointed out previously, there is a certain amount of overlap in their clinical manifestations [88].

MCTD myositis is associated with other systemic features of systemic sclerosis or SLE such as Raynaud's phenomenon, sclerodactyly and synovitis, and there are high titres of antibodies to a 70-kD ribonuclear protein complex (anti-U1 snRNP). The scleroderma-myositis overlap occurs in only a small minority of cases of scleroderma and is characterised by the presence of antibodies to the nucleolar PM-Scl antigen complex (anti-PM-Scl), which is rare in scleroderma and other forms of myositis but, when present, is a strong marker for the scleroderma-myositis overlap syndrome [84].

In the antisynthetase syndrome, which is associated with antibodies to one of the tRNA synthetases, myositis is accompanied by other systemic features including interstitial lung disease, Raynaud's phenomenon, deforming arthropathy and skin changes in the hands, and the condition is relatively resistant to treatment [117]. The most prevalent antisynthetase antibody is anti-Jo-1 (anti-histidyl tRNA synthetase), which is present in about 20% of cases of PM and DM [118-120]. Pathologically, perimysial connective tissue damage with associated CD68+ histiocytes, perivascular CD4+ T cells and perifascicular fibre necrosis and regeneration are described in cases with anti-Jo-1 [1, 121]. Other rarer antisynthetases associated with this syndrome include anti-PL-12 (alanyl-tRNA synthetase), anti-PL-7 (threonyl-tRNA synthetase), anti-EJ (glycyl-tRNA synthetase), anti-OJ (isoleucyl-tRNA synthetase), anti-KS (asparaginyl-tRNA synthetase), anti-Zo (phenylalanyl-tRNA synthetase) and anti-Ha (tyrosyl-tRNA synthetase) [122].

#### **4. Immune-mediated necrotising myopathies (IMNM)**

The IMNMs are a heterogeneous group of acquired myopathies which are distinguishable from DM and PM on clinical and pathological grounds, and are amenable to treatment with immune therapies [123]. As shown in Table 3, they can be classified into a number of different categories, including cases associated with malignancy, connective tissue disease or viral infections, and those associated with specific autoantibodies such as anti-SRP, anti-HMGCR and antisynthetase antibodies which are putatively involved in the pathogenesis of the necrotising myopathy. Although inflammation is usually lacking (Fig 4), IMNM is considered to be autoimmune in nature because of immunostaining for C5b-9 and MHC-I in some

cases, association with autoantibodies and other immune disorders, and response to immune therapy [124].

Table 3 Potential triggers for immune-mediated necrotising myopathies

Anti-signal recognition particle antibodies
Statin therapy (anti-HMGCR antibodies)
Antisynthetase antibodies
Malignancy
Connective tissue diseases
Viral infections (HIV, hepatitis C)

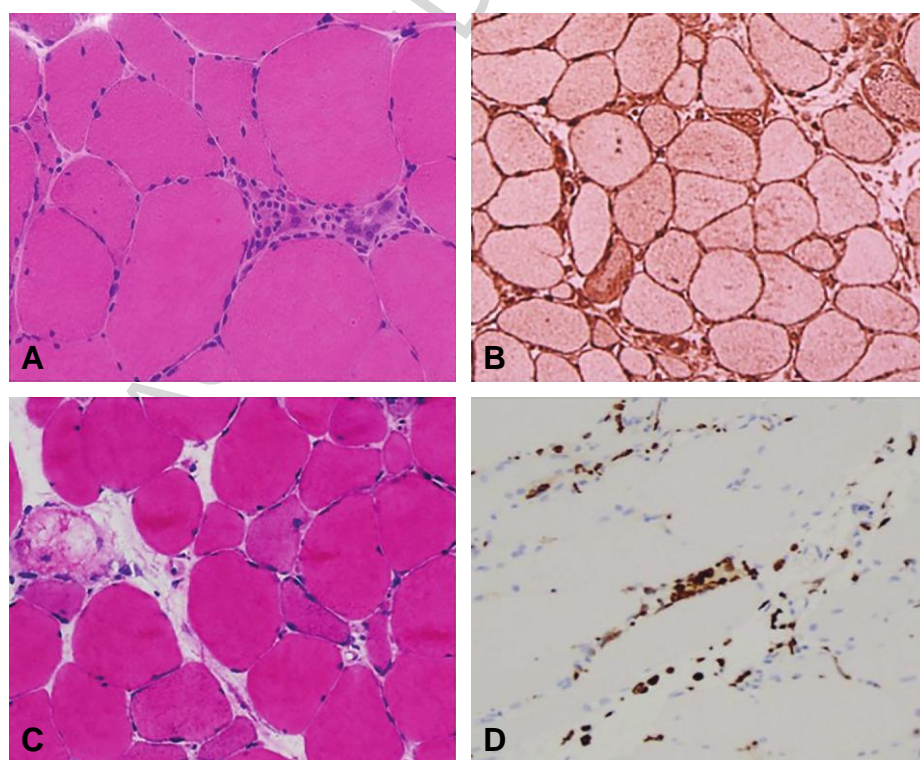


Figure 4 Immune-mediated necrotising myopathy (A & B associated with prolonged statin therapy; C & D idiopathic case): (A) Muscle fibre necrosis with sparse inflammatory infiltrate; (B) Diffuse sarcolemmal and sarcoplasmic MHC-I expression; (C) Necrotising myopathy with (D) scattered macrophagic infiltrate. A & C:

haematoxylin and eosin; B and D: MHC-I and CD163 immunohistochemistry respectively.

#### *4.1 Myopathy associated with anti-SRP antibody*

The anti-signal-recognition-particle (SRP) antibody was previously considered as one of the group of myositis-specific antibodies that are associated with PM or DM [125, 126]. This notion has since changed and myopathy with anti-SRP antibody now stands as a separate entity which is distinguishable from PM and DM, and which is less frequently associated with other concomitant autoimmune or connective tissue diseases. It is characterised clinically by rapidly progressive and at times more chronic proximal muscle weakness, with high serum CK levels, and relative resistance to treatment with conventional immune therapies, and pathologically by an active necrotising myopathy, with a relatively inconspicuous or absent inflammatory infiltrate, and a predominance of macrophages [15]. In contrast to PM and DM, muscle inflammation is never a dominant feature in SRP-associated myopathy and up-regulation of MHC-I antigen is not a consistent finding. The observation of a correlation between serum levels of the antibody and CK levels, and that following plasmapheresis antibody titres fall as clinical improvement occurs, favours a causal role for the antibody [127]. The finding in some cases of C5b-9 deposition on endomysial capillaries and non-necrotic muscle fibres [126] suggests that a complement-dependent antibody-mediated mechanism of muscle fibre injury may be involved.

SRP is a cytoplasmic ribonucleoprotein complex that transfers newly synthesised peptides that are destined for secretion or membrane localisation from ribosomes to the ER for further processing [128]. It is composed of a 7SL RNA sequence and six protein units with molecular weights of 9, 14, 19, 54, 68 and 72kDa respectively. The anti-SRP antibody associated with necrotising myopathy mainly targets the 54kDa protein that binds to the nascent polypeptides emerging from the ribosome as well as the SRP receptors on the endoplasmic reticulum membrane [129].

It is not clear how the anti-SRP antibody leads to muscle fibre necrosis, or why muscle is predominantly affected when the SRP is ubiquitously expressed. The anti-SRP antibody has been shown to interfere with the association of SRP and the

signal sequence of the peptide, as well as the SRP receptor-mediated peptide translocation to the endoplasmic reticulum [129] and would be expected to disrupt the translation and post-translational processing of a large range of proteins. Proteomic studies on patients with SRP-associated myopathy would be able to clarify this issue. A recent study has demonstrated anti-SRP antibody binding and associated complement products on the surface of muscle fibres in biopsies from cases of anti-SRP associated IMNM [130]. In the same study it was also shown that incubation of human myoblast cultures with anti-SRP positive sera lead to aberrant expression of the SRP protein on the surface of myoblasts and induced cell lysis through a complement-dependent process. These findings point strongly to an antibody-mediated complement-dependent mechanism of muscle fibre injury in anti-SRP associated IMNM.

#### *4.2 Anti-HMGCR associated myopathy*

Statins, or 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMGCR) inhibitors, have long been known to cause a spectrum of muscle symptoms ranging from simple myalgia to a more severe necrotising myopathy, and at times even fatal rhabdomyolysis [131]. The risk of myopathy varies with the different statins and predisposing factors include age, female gender, and other co-morbidities and concomitant medications. In addition, the importance of genetic predisposition is being increasingly recognised and has been reviewed recently [132]. The genes so far identified that can influence susceptibility to statin myopathy include: *SLCO1B1* (which encodes an anion transmembrane hepatic statin transporter protein) [133]; *CYP2D6* and *CYP3A5* (hepatic cytochrome P450 2D6 and 3A5 enzymes that metabolize statins) [134, 135]; *EYS* (eyes shut homologue that is involved in the Notch pathway) [136]; *ABCB1* (the efflux transporter p-glycoprotein) [137, 138]; and *GTAM* (glycine amidinotransferase that participates in the synthesis of creatine) [139]. Several pathomechanisms have been proposed for statin myotoxicity, including reduced cholesterol levels [140], impaired post-translational processing (prenylation and glycosylation) of proteins [141], coenzyme Q<sub>10</sub> deficiency [142], mtDNA depletion [143], disturbance of the ubiquitin-proteasome and lysosomal pathways [144, 145], and activation of apoptosis [146].



While the majority of cases of statin myopathy are self-limiting, and there is progressive improvement of muscle symptoms and normalisation of CK levels once the statin is discontinued, it is now recognised that a small subgroup of patients who develop an IMNM symptoms continue to progress, or may even first develop after the statin is withdrawn [147]. In these patients, an autoimmune process is initiated, as demonstrated by the presence of a highly specific anti-HMGCR antibody which targets the cytoplasmic domain of HMGCR [148] and which is not found in patients with other forms of statin myopathy [149, 150]. The levels of the antibody correlate with serum CK levels as well as upper limb strength, making it a suitable marker for disease activity [151]. It is noteworthy that the antibody may also be found in some patients without prior statin exposure [148]. It was also found that the expression of HMGCR is up-regulated in regenerating muscle fibres in biopsies from anti-HMGCR-positive patients (Fig 5) and it was postulated that the persistent overexpression of the autoantigen may be responsible for sustaining the autoimmune process even after the statin is withdrawn. MHC-I antigen has been shown to be up-regulated on the surface of non-necrotic fibres of statin-associated IMNM [152], but statin alone does not induce over-expression of MHC-I *in vitro*, suggesting synergistic effects of other unknown factors [153]. The *HLA-DR1\*11:01* allele is associated with the development of anti-HMGCR antibody-positive IMNM, suggesting a role of the molecule encoded by this allele in the antigen-presentation process [154].

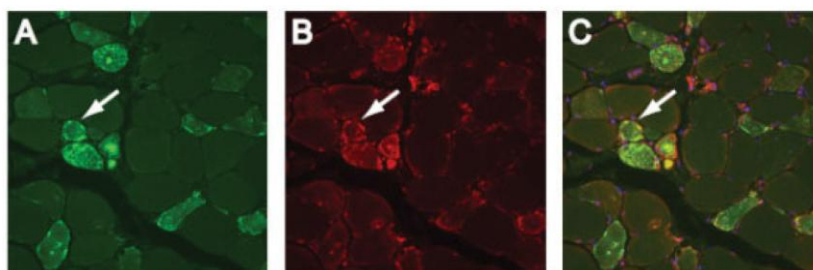


Figure 5 Up-regulation of HMGCR antigen in regenerating muscle fibres (arrows) in anti-HMGCR associated myopathy: A. Anti-NCAM antibody; B. Anti-HMGCR antibody; C. Overlay image. (Courtesy of Dr A. Mammen and the publisher [138]).



#### *4.3 IMNM associated with antisynthetase antibodies*

Patients with antibodies to histidyl tRNA synthetase (Jo-1) or the other tRNA synthetases may also develop IMNM, with symptoms of myalgia or muscle weakness and high serum CK, with or without other features of the antisynthetase syndrome such as interstitial lung disease, arthropathy and skin changes [123]. Pathological descriptions include a necrotising myopathy with a macrophage predominant endomysial and perimysial infiltrate and connective tissue fragmentation, MHC-I expression and capillary and sarcolemmal deposition of MAC [121]. However further documentation is required to determine how consistent the pathological phenotype is and if such cases represent a separate entity or are merely part of a spectrum of disorders associated with antisynthetase antibodies.

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